APPLICANT'S REMARKS

1. Status of the Claims

With entry of this Amendment, claims 1, 3, 10, 12, and 15 are pending. Claims 1, 13, 10, and 12 are currently amended. Claim 15 is new. Claims 2, 4–9, 11, 13, and 14 are canceled.

2. Withdrawal of Rejections based on VETTER or GROHE

The Applicant gratefully acknowledges that the Examiner has withdrawn all rejections based on VETTER or GROHE.

3. Rejection of claims 1–3 and 9–14 under 35 U.S.C. 112, 2nd paragraph

Claims 1–3 and 9–14 are rejected under under 35 U.S.C. 112, 2nd paragraph. The Examiner asserts that the phrase "solid betaine of the formula III" renders those claims indefinite because it is unclear if the claims define a "betaine salt," i.e., a salt with trimethylglycine (a.k.a., glycine betaine or betaine).

In order to advance the prosecution of this application, the claims are amended to recite "ciprofloxacin betaine or enrofloxacin betaine." The Applicant respectfully submits that one skilled in the art would clearly understand the meaning of ciprofloxacin betaine and enrofloxacin betaine.

"The test for definiteness under 35 U.S.C. § 112, second paragraph, is whether 'those skilled in the art would understand what is claimed when the claim is read in light of the specification.'" *Ex parte* Miyazaki, 89 USPQ2d 1207 (BPAI 2008) *quoting* Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1576 (Fed. Cir. 1986) (citations omitted). "The person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313. It is appropriate "to rely heavily on the written description for guidance as to the meaning of the claims." Id. at 1317.

The ordinary and customary meaning of a term may be evidenced by a variety of sources, including "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." (Phillips v. AWH Corp., 415 F.3d at 1314, 75 USPQ2d at 1327). If extrinsic reference sources, such as dictionaries, evidence more than one definition for the term, the intrinsic record must be consulted to identify which of the different possible definitions is most consistent with applicant's use of the terms. Brookhill-Wilk 1, 334 F. 3d at 1300, 67 USPQ2d at 1137; *see also* Renishaw PLC v. Marposs Societa" *per* Azioni, 158 F.3d 1243, 1250, 48 USPQ2d 1117, 1122 (Fed. Cir. 1998) ("Where there are several common meanings for a claim term, the patent disclosure serves to point away from the improper meanings and toward the proper meanings.") *and* Vitronics Corp. v. Conceptronic Inc., 90 F.3d 1576, 1583, 39 USPQ2d 1573, 1577 (Fed. Cir. 1996) (construing the term "solder reflow temperature" to mean "peak reflow temperature" of solder rather than the "liquidus temperature" of solder in order to remain consistent with the specification.). Extrinsic sources may not be used

to contradict claim meaning that is unambiguous in light of the intrinsic evidence. See Id. at 1322. See Vitronics at 1583-84; Intel Corp. v. VIA Techs., Inc., 319 F.3d 1357, 1367 (Fed. Cir. 2003).

Therefore, the Applicant respectfully urges the Examiner to read the terms "ciprofloxacin betaine" and "enrofloxacin betaine" in the context of the claims, the specification, and the prosecution history, as well as the extrinsic evidence. The Examiner is mistaken to rely on an IUPAC definition without considering how that extrinsic definition compares with the intrinsic evidence, *i.e.*, the claims, specification, and prosecution history.

From the specification, claims, and prosecution history, one skilled in the art would understand the meaning of ciprofloxacin betaine and enrofloxacin betaine. For example, ciprofloxacin betaine as described and claimed cannot be a salt form with trimethylglycine because ciprofloxacin betaine may be converted into the salt-forms ciprofloxacin embonate and ciprofloxacin hemi-embonate (see paragraph 28–31 in the present specification). Significantly, the Applicant uses the term "betaine" in contrast to ciprofloxacin hydrochloride (see the table in paragraph 43).

Moreover, the IUPAC definition for "betaine" states, in relevant part:

> Originally, the compound betaine, $(CH3)3N^{+}–CH_2C(=O)O^{-}$ N,N,N-trimethylammonioacetate, and similar zwitterionic compounds derived from other amino acids. By extension, neutral molecules having charge-separated forms with an onium atom

which bears no hydrogen atoms and that is not adjacent to the anionic atom.

In light of this extrinsic evidence, ciprofloxacin betaine and enrofloxacin betaine cannot be salt forms with trimethylglycine because a "betaine" is a zwitterionic compound.

In light of the foregoing, the Applicant respectfully requests reconsideration and withdraw of the rejection of claims 1 and 14 based on 35 U.S.C. 112, 2nd paragraph.

2. Rejection of Claims 1, 2, and 14 under 35 U.S.C. 102(e) based on PILKEIWICZ

Claims 1, 2, and 14 were rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Published Patent Application No. 2004/0009126 (PILKIEWICZ). The Examiner asserts that PILKEIWICZ teaches a method of treating bacterial lung infection comprising local administration of ciprofloxacin by inhalation, wherein the ciprofloxacin is in the form of particles and may be in the form of dry powder.

The Applicant respectfully disagrees with the Examiner and asserts that the present claims are not anticipated by PILKEIWICZ because, for example, PILKEIWICZ only teaches (*i.e.*, enables) a water-soluble form of ciprofloxacin entrapped in liposomes, which is clearly distinguishable from the insoluble betaines (and slightly soluble salts thereof) recited by the current claims.

In response to Applicant's previous remarks concerning this 102(e) rejection, the Examiner states that "disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi…"

The Applicant respectfully submits that the question is not whether PILKIEWICZ "teaches away" from the present claims, but whether PILKIEWICZ *teaches* one of ordinary skill in the art to make or carry out the claimed invention without undue experimentation (Elan Pharmaceuticals, Inc. v. Mayo Foundation, 346 F.3d 1051, 1054-55 (Fed. Cir. 2003) (anticipation requires enablement)). In fact, "teaching away" is irrelevant to anticipation. Seachange International, Inc., v. C-Cor, Inc., 413 F.3d 1361, 1380 (Fed. Cir. 2005).

The Applicant respectfully submits that PILKIEWICZ only teaches (*i.e.*, enables) liposomal ciprofloxacin. PILKIEWICZ only exemplifies liposomal ciprofloxacin, and does not reasonable suggest any other kind of ciprofloxacin particle.

Specifically, the making of liposomal ciprofloxacin is described in Example 2 of PILKIEWICZ at paragraphs 72 to 74. According to PILKIEWICZ, a 16 mg/ml "stock Cipro solution" was used to made liposomal ciprofloxacin (paragraph 73). The "stock Cipro solution," at 16 mg of ciprofloxacin per ml of water, is a solution comprising a water-soluble form of ciprofloxacin, such as, perhaps, ciprofloxacin hydrochloride.

In the Final Office Action, the Examiner asserts that "there is no evidence in Pilkiewicz reference [that] shows that the so called CIPRO stock solution is a water solution of ciprofloxacin hydrochloride."

The Applicant directs the Examiner to paragraph 72 of PILKIEWICZ that describes preparation of "16 mg/ml stock Cipro solution in citrate buffer at pH 5."

The Examiner further notes "that Pilkiewicz claims the composition comprises an antiinfective agent of claim 1, without the requirement that the agent be a salt…[and therefore] Pilkiewicz clearly teaches the employment of non-salt form[s] of antiinfective agent[s]."

The Applicant respectfully submits that the question of enablement cannot be answered by reference to the claims alone. The question of enablement requires reference to the entire specification.

According to PILKIEWICZ at paragraph 59:

> As shown in FIG. 2, liposomal ciprofloxacin administered intratracheally is maintained at a high level in the lungs for two hours whereas the lung levels of free ciprofloxacin delivered intratracheally were negligible after one hour…Thus liposomal ciprofloxacin given by inhalation is more advantageous with respect to targeting and retention in the lung than free ciprofloxacin given either by inhalation or orally.

These test results are also discussed at paragraph 74.

Therefore, one skilled in the art, reading PILKIEWICZ as a whole, would understand that a powder comprising liposomal-entrapped, water-soluble ciprofloxacin is superior to un-entrapped, water-soluble ciprofloxacin for delivery to the lungs as a treatment for intracellular infections.

The Applicant respectfully submits that PILKIEWICZ, in fact, does not indicate any reason for using an insoluble form of ciprofloxacin. PILKIEWICZ does not contemplate using an insoluble form of ciprofloxacin, or even suggest that using an insoluble form of ciprofloxacin might be possible.

In contrast to PILKIEWICZ, the present independent claim 1 recites a method of treating a bacterial disease of the lungs in humans and animals by locally administering an antibacterially effective amount of a solid ciprofloxacin betaine or enrofloxacin betaine, or a solid slightly soluble salt thereof, in a powder form or powder-containing suspension.

Ciprofloxacin betaine and enrofloxacin betaine are non-salt forms that are quite insoluble in water. For example, the solubility of ciprofloxacin betaine in water is less than about 0.1 mg/ml (*see* CAÇO et al. submitted with the accompanying I.D.S.) These betaines may be transformed into slightly soluble salts, such as mono-embonate or hemi-embonate salts. The phrase "slightly soluble" is defined by the present specification as: a solubility in water at 25°C of less than 0.1% by weight.

Therefore, PILKIEWICZ does not teach (*i.e.*, enable) or even suggest all the features of the invention as recited in claims 1, 2, and 14. Accordingly, the Applicant respectfully submits that the 35 U.S.C. 102(e) rejection of claims 1, 2, and 14 based on PILKIEWICZ should be reconsidered and withdrawn.

3. Rejection of Claims 1, 2, and 14 under 35 U.S.C. 103(a) based on MAYER and LI

Claims 1, 2, and 14 were rejected under 35 U.S.C. 103(a) as being unpatentable over MAYER et al., *Clinical Presentation of Inhalation Anthrax Following Bioterrorism Exposure*, in view of LI et al., *Ciprofloxacin-loaded bovine serum albumin microspheres: preparation and drug release* in vitro. The Examiner argues that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use a dry powder inhaler for delivery of a ciprofloxacin composition of LI directly to the respiratory track for treatment of a respiratory track bacterial infection.

The Applicant respectfully disagrees with the Examiner and asserts that the present claims are not obvious based on the combination of MEYER and LI. Even assuming, *arguendo*, that the references were properly combined, the cited combination does not provide or even suggest the features of the invention recited in the present claims.

Specifically, the cited combination does not provide or even suggest a method for controlling bacterial diseases of the respiratory organs in humans and animals by locally administering an

antibacterially effective amount of solid ciprofloxacin betaine or enrofloxacin betaine, or a solid slightly soluble salt thereof, in a powder form or powder-containing suspension.

In response to Applicant's previous remarks concerning this 103(a) rejection, the Examiner states that the "Li reference never teach[s] or suggest[s] that the ciprofloxacin has to be in salt form or be water soluble."

Contrary to the Examiners assertion, LI teaches that the ciprofloxacin must be water soluble at page 825, in the abstract ("The spherical microspheres…were organic solvent solvent free"), and page 826, paragraph 2 ("CIPRO was dissolved in distilled water and different amounts of bovine serum albumin were added into the filtered aqueous solutions of CIPRO for spray drying.").

The Applicant respectfully submits that LI, in fact, does not indicate any reason for using an insoluble form of ciprofloxacin. LI does not teach using an insoluble form of ciprofloxacin, or reasonably suggest using an insoluble form of ciprofloxacin.

MEYER is cited only for the proposition that ciprofloxacin is useful to treat bacterial infections in the lungs (*i.e.*, inhalational anthrax). MEYER, as acknowledged by the Examiner, does not teach the local administration of an antibiotic, but rather parental administration. Also, the particular ciprofloxacin formulation used by MEYER is undisclosed.

Unlike the cited combination of MEYER and LI, the present independent claims 1 and 14 recite a method for controlling bacterial diseases of the respiratory organs in humans and animals by

locally administering an antibacterially effective amount of solid ciprofloxacin betaine or enrofloxacin betaine, or a solid slightly soluble salt thereof, in a powder form or powder-containing suspension.

Again, ciprofloxacin betaine and enrofloxacin betaine are non-salt forms that are only slightly soluble in water. These betaines may be transformed into slightly soluble salts, such as ciprofloxacin mono-embonate or ciprofloxacin hemi-embonate. The phrase "slightly soluble" is defined by the present application as: a solubility in water at 25°C of less than 0.1% by weight.

In light of the foregoing, the Applicant respectfully requests reconsideration and withdraw of the 35 U.S.C. 103(a) rejection of claims 1, 2, and 14 based on MAYER and LI.

5. Rejection of Claims 1, 2, and 14 under 35 U.S.C. 103(a) based on PILKIEWICZ and KANIKANTI

Claims 1, 2, and 14 were rejected under 35 U.S.C. 103(a) as being unpatentable over PILKIEWICZ in view of U.S. Pub. Pat. App. No. 2004/0024018 (KANIKANTI). The Examiner argues that one skilled in the art at the time of the invention would have combined ciprofloxacin betaine (as provided by KANIKANTI) with the PILKIEWICZ method.

The Applicant respectfully disagrees with the Examiner and submits that the references are not properly combined. First, attempting to combine the insoluble ciprofloxacin betaine of KANIKANTI with the liposomes of PILKIEWICZ would change the basic principle of operation

of PILKIEWICZ. As discussed above, PILKIEWICZ teaches liposomal formulations of water-soluble ciprofloxacin. In contrast, ciprofloxacin betaine of KANIKANTI is a slightly water-soluble non-salt form of ciprofloxacin. Second, one skilled in the art would have no expectation that PILKIEWICZ could be successfully combined with KANIKANTI. PILKIEWICZ gives no reason to use an insoluble form of ciprofloxacin of KANIKANTI or even suggest that it could be possible to use an insoluble form of ciprofloxacin.

The Applicant respectfully requests that the 35 U.S.C. 103(a) rejection of claims 1, 2, and 14 based on PILKIEWICZ and KANIKANTI be reconsidered and withdrawn.

6. Rejection of Claims 1, 2, 14 under 35 U.S.C. 103(a) based on MEYER, LI, and KANIKANTI

Claims 1, 2, and 14 were rejected under 35 U.S.C. 103(a) as being unpatentable over MAYER and LI, and further in view of KANIKANTI.

The Applicant respectfully disagrees with the Examiner and submits that the references are not properly combined. First, attempting to combine the insoluble ciprofloxacin betaine of KANIKANTI with the microspheres of LI would change the basic principle of operation of LI. As discussed above, LI teaches microsphere formulations of water-soluble ciprofloxacin. In contrast, ciprofloxacin betaine of KANIKANTI is the slightly soluble non-salt form of ciprofloxacin. Second, one skilled in the art would have no expectation that LI could be successfully combined with KANIKANTI. LI gives no reason to use an insoluble form of

ciprofloxacin of KANIKANTI or even suggest that it could be possible to use an insoluble form of ciprofloxacin.

In light of the foregoing, the Applicant respectfully requests reconsideration and withdraw of the 35 U.S.C. 103(a) rejection of claims 1, 2, and 14 based on MAYER, LI, and KANIKANTI.

8. Conclusion

The Applicant respectfully requests favorable consideration and that this application be allowed.

Respectfully submitted,

Date: June 21, 2010

/THOMAS C. BLANKINSHIP/

Thomas C. Blankinship
Reg. No. 39,909